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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/954,556	09/14/2001	Brett P. Monia	RTS-0250	7962

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/26/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/954,556	MONIA ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10 and 12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4-10, and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office Action is a response to the Election filed June 10 2003, in Paper No. 9 and the Amendment filed April 4, 2003 in Paper No. 7.

Claims 1, 2, 4-10, and 12-15 are pending in the instant application.

Claims 3, 11 and 16-20 have been canceled. Claims 1 and 10 have been amended. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

Claims 1, 2, 4-10, and 12-15 have been examined on the merits.

Election/Restrictions

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's election with traverse of the coding region of SEQ ID NO: 3, in Paper No. 9 is acknowledged. The traversal is on the ground(s) that all of the claims are related to the single concept of modulating the expression of fibroblast growth factor receptor 2. Further, Applicant argues that the sequences recited are patentable, novel and unobvious over each other. Applicants also argue that a search of literature relating to one target region claimed would not alter the search burden on the Office since the entire sequence has already been necessarily searched. Applicants further argue that a search of literature relating to one target region claimed would include the entire sequence of human fibroblast growth factor receptor 2, SEQ ID NO: 3. Applicants also argue that restricting the sequences into target regions of multiple individual

applications for examination is contrary to the intent of the Commissioner to provide efficient cost-effective examination of inventions relating to biotechnology inventions comprising nucleotide sequences.

Applicants arguments have been fully considered, but are not found persuasive because as argued in the restriction requirement (Paper No. 8), although the compounds claimed each targets the expression of the same gene, the compounds targeting the recited target region are considered to be unrelated, since each compound claimed is structurally and functionally independent and distinct for the following reasons: Each compound has a unique nucleotide sequence corresponding to the recited target region, each compound targets a different and specific region of a nucleic acid encoding human fibroblast growth factor receptor 2, and each compound, upon binding to a nucleic acid encoding human fibroblast growth factor receptor 2, functionally modulates (increases or decreases) the expression of the gene. Furthermore, a search of more than one (1) of the target region sequences recited in claim 1 presents an undue burden on the Patent and Trademark Office due to the complex nature of the search and corresponding examination of more than one (1) of the claimed sequences. In summary, since each compound claimed is structurally and functionally independent and distinct, and since a search of more than one of the target region sequences recited in claim 1 presents an undue burden on the Patent and Trademark Office due to the complex nature of the search, one region is considered to be reasonable for examination.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound 8 to 50 nucleotides in length that targets and inhibits the expression of fibroblast growth factor receptor 2 *in vitro*, does not reasonably provide enablement for a method of treating human having a disease or condition associated with fibroblast growth factor receptor 2 via a compound 8 to 50 nucleotides in length that targets and inhibits the expression of fibroblast growth factor receptor 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection is maintained for the reasons of record set forth in the Office Action mailed January 2, 2003 in Paper No. 6.

Applicants disagree that the application of antisense *in vivo* is unpredictable. Applicants argue that the references cited by the Examiner to support the position that the application of antisense *in vivo* is unpredictable actually teach the potential usefulness of antisense drugs in humans and fail to provide any reasonable basis to doubt the pharmacological activity observed in cells would not occur in animals and humans. Applicants argue that Jen and Gewirtz (2000) is a review paper on the evolution of technology to suppress gene expression, including antisense technology and its use in human disease, but does not suggest that antisense compounds would be inherently unpredictable *in vivo*. Applicants argue that Branch (1998) teaches the need to develop antisense molecules based on sound data and careful screening, but does not suggest that extrapolation from *in vitro* data to *in vivo* effects is unpredictable. Applicants argue that to

advance the prosecution of the instant application, claims 16-20 have been canceled and the rejection should be withdrawn.

Applicant's arguments have been fully considered, but are not found persuasive because claim 15 reads on a method of inhibiting the expression of fibroblast growth factor receptor 2 *in vitro* or *in vivo*. Applicants have not furnished any evidence to support of their argument that the application of antisense *in vivo* is predictable. While Applicants argue that Jen and Gewirtz and Branch report some progress in antisense therapies, the cited publications also indicate that such successes are not the rule, but few and far between. Furthermore, the cited publications of Jen and Gewirtz and Branch are review publications and are an indicator of the true state of the art of antisense technology as it relates to *in vivo* use. Because of the unpredictability of the art and the specification's lack of particular guidance or particular direction, the quantity of experimentation required of one of skill in the art to practice the instant invention would include the de novo determination of how to engineer and deliver an antisense targeting fibroblast growth factor receptor 2 *in vivo,* such that fibroblast growth factor receptor 2 is inhibited to any degree. Therefore, undue experimentation would be required of one of skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 102

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Wilson, S. (GenEmbl Accession No. I32954). This rejection is maintained for the reasons of record set forth in the Office Action mailed January 2, 2003 in Paper No. 6.

Applicants have amended claim 1 to read on a compound 8 to 50 nucleobases in length targeted to the coding region of a nucleic acid molecule encoding human fibroblast growth factor receptor 2 (SEQ ID NO: 3). Applicants argue that Wilson et al. disclose a 30 base pair fibroblast growth factor receptor 2 downstream primer and probe which is 100% complementary to nucleobases 1242 through 1271 of SEQ ID NO:3, but does not teach or suggest any antisense sequences as now claimed which are targeted to the coding region of a nucleic acid molecule encoding human fibroblast growth factor receptor 2 (SEQ ID NO: 3).

Applicant's arguments have been fully considered, but are not found persuasive because as Applicants point out, Wilson et al. disclose a 30 base pair fibroblast growth factor receptor 2 downstream primer and probe which is 100% complementary to nucleobases 1242 through 1271 of SEQ ID NO:3. It is noted that nucleobases 1242 through 1271 fall within the coding region of fibroblast growth factor receptor 2 (SEQ ID NO: 3).

Since the prior art oligonucleotide meets all the structural limitations of the claims, the prior art oligonucleotides would then be considered to "inhibit expression" of the gene as claimed, absent evidence to the contrary. See, for example, MPEP § 2112, which states "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. 'There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.' In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic.

Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims." Therefore, Wilson et al. anticipate claim 1.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Wilson, S. (GenEmbl Accession No. I87104). This rejection is maintained for the reasons of record set forth in the Office Action mailed January 2, 2003 in Paper No. 6.

Applicants argue that Wilson et al. disclose a 30 base pair fibroblast growth factor receptor 2 downstream primer and probe which is 100% complementary to nucleobases 1242 through 1271 of SEQ ID NO:3, but does not teach or suggest any antisense sequences as now claimed which are targeted to the coding region of a nucleic acid molecule encoding human fibroblast growth factor receptor 2 (SEQ ID NO: 3).

Applicant's arguments have been fully considered, but are not found persuasive because of the explanation given above for the 35 U.S.C. 102(b) rejection against claim 1 as being anticipated by Wilson, S. (GenEmbl Accession No. I32954). Therefore, Wilson et al. (GenEmbl Accession No. I87104) anticipate claim 1.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Chenchik et al. (GenEmbl Accession No. AR090312). This rejection is maintained for the reasons of record set forth in the Office Action mailed January 2, 2003 in Paper No. 6.

Applicants argue that Chenchik et al. disclose a 30 base pair fibroblast growth factor receptor 2 downstream primer and probe which is 100% complementary to nucleobases 1179 through 1203 of the coding region of SEQ ID NO:3, but does not teach or suggest any antisense

sequences as now claimed which are targeted to the coding region of a nucleic acid molecule encoding human fibroblast growth factor receptor 2 (SEQ ID NO: 3).

Applicant's arguments have been fully considered, but are not found persuasive because of the explanation given above for the 35 U.S.C. 102(b) rejection against claim 1 as being anticipated by Wilson, S. (GenEmbl Accession No. I32954). Therefore, Chenchik et al. anticipate claim 1.

Claims 1, 2, 4, 5, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamada et al. (Glia, 1999 Vol. 28:66-76). This rejection is withdrawn in view of Applicants arguments filed April 4, 2003 in Paper No. 8. However, it is noted that the Examiner does not have any evidence of the specific nucleotide sequence or length of the antisense oligonucleotide of Yamada et al. Applicant is reminded of their duty to disclose (see 37 CFR 1.56 - Duty to disclose information material to patentability). If Applicants have any information regarding the nucleotide sequence or length of the antisense oligonucleotide of Yamada et al. or if the Examiner discovers any information regarding the antisense oligonucleotide of Yamada et al., it is noted that this information may be used as art in subsequent Office Actions.

Claim Rejections - 35 USC § 103

Claims 1, 2, 4-10, and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamada et al. (Glia, 1999 Vol. 28:66-76), in further view of Baracchini et al. [U.S. Patent

No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288). This rejection is withdrawn in view of Applicants arguments filed April 4, 2003 in Paper No. 8.

Claims 1, 2, 4-10, and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamada et al. (Glia, 1999 Vol. 28:66-76), in further view of Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288).

Claim 1 as now amended is drawn to a compound 8 to 50 nucleobases in length targeted to the coding region of a nucleic acid molecule encoding fibroblast growth factor receptor 2 (SEQ ID NO: 3), wherein the compound specifically hybridizes with the nucleic acid molecule and inhibits the expression of fibroblast growth factor receptor 2. Claims 2, 4-10, and 12-15 depend from claim 1 and include all the limitations of claim 1 including modifications to the compound and methods of inhibiting fibroblast growth factor receptor 2 in cell or tissues with said compound.

Yamada et al. teach the suppression of glioblastoma cell growth following antisense oligonucleotide-mediated inhibition of fibroblast growth factor receptor 2 expression. Yamada et al. further disclose a phosphorothioate antisense oligonucleotide complementary to the translation start site of fibroblast growth factor receptor 2 reduced cell growth in cultured human neuroblastoma cells (see page 69, last paragraph and Figure 3).

Yamada et al. do not teach a compound 8 to 50 nucleobases in length targeted to the coding region of a nucleic acid molecule encoding fibroblast growth factor receptor 2 or a compound comprising an antisense oligonucleotide further comprising at least one modified

sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide; and a composition comprising a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding fibroblast growth factor receptor 2 and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system.

Baracchini et al. teach antisense oligonucleotide compounds of 8 to 50 nucleobases in length can be synthesized to a preferred gene of interest to modulate gene expression (see column 8, lines 57-62). It is also well known in the art that an antisense oligonucleotide of 8 to 50 nucleobases in length is a conventional size range for optimal binding of a gene of interest. Baracchini et al. also teach the synthesis and use of antisense oligonucleotides targeted to preferred target regions such as the coding region (see column 9, lines 6-67 and column 10, lines 1-25). Baracchini et al. further teach modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases. Baracchini et al. further teach antisense oligonucleotides with phosphorothioate-modified backbones (see column 6, line 37)... with at least one modified sugar moiety and a modified 2'-O-methoxyethyl sugar moieties (see Table I)... with modified nucleobases, such as 5-methylcytosine (see column 7, lines 15-25). Baracchini et al. finally teach an antisense oligonucleotide as a chimeric oligonucleotide (see column 8, lines 12-19)

Fritz et al. teach a composition comprising an antisense oligonucleotide and a pharmaceutically acceptable carrier or diluent comprising a colloidal dispersion system. Fritz et

al. further teach that oligonucleotides, in combination with steric stabilizers, exhibit high colloidal stability with low toxic side effects as required for biological experiments in cell culture and *in vivo* (see page 287, last paragraph).

It would have been obvious to make antisense oligonucleotides targeting fibroblast growth factor receptor 2 since the prior art has asserted that fibroblast growth factor receptor 2 is involved in the cell growth of neuroblastoma cells (Yamada et al.). One of ordinary skill in the art would have been motivated to make antisense oligonucleotides targeting fibroblast growth factor receptor 2 since the prior art taught the desire to reduce endogenous fibroblast growth factor receptor 2 protein and mRNA by antisense techniques. One of ordinary skill would have expected success in making a compound 8 to 50 nucleobases in length targeted to the coding region of a nucleic acid molecule encoding fibroblast growth factor receptor 2 following the method of Baracchini et al. One of ordinary skill in the art would have been motivated to make a compound 8 to 50 nucleobases in length targeting the coding region since Baracchini et al. taught antisense oligonucleotides 8 to 50 nucleobases in length can optimally modulate gene expression and because it is well known in the art to target different sites within a gene for the oligonucleotide interaction to occur such that desired effect, e.g., detection or modulation of expression of the protein, will result. One of ordinary skill in the art would have been motivated to modify antisense oligonucleotides since the prior art has taught the desirability of such oligonucleotides are often preferred over native forms because of enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases and the exhibition of high colloidal stability with low toxic side effects as required for biological experiments (Baracchini et al. and Fritz et al.).

Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg

KAREN LACOURCIERE
PATENT EXAMINER